## REMARKS

Claims 21-82 are pending in the application. It is noted that in the Advisory Action that the Examiner indicates claims 21-26 and 32-34 are allowed, claims 38 and 39 are objected to and claims 27-31, 35-37 and 40-82 are rejected. As the response filed on November 16, 2000 was not entered, Applicant has repeated the arguments presented in that response, has included additional arguments that are specifically responsive to issues highlighted by the Examiner and has corrected the claim amendments to overcome the confusion noted by the Examiner. Applicant notes that the Examiner stated that the response filed on November 16, 2000 overcame the prior art rejections. Claim 21,44 and 66 have been amended to insert "and" after step (A) and to delete "and" in claims 21 and 66, before "(iii)" of step (A). Claim 63 has been amended to more clearly define the present invention. The amendment to claim 63 has support on page 13, line 29. Applicant kindly requests the entry of this amendment as it does not raise any new issues and places the claims in better condition for appeal, and is responsive to the issues raised in the Advisory Action. Applicant respectfully requests review and reconsideration of the pending claims in view of the foregoing amendments and following remarks as well as the remarks provided in the response filed on November 29, 1999.

In the April 14, 2000, Office Action, claims 27-31, 35-37, and 40-82 were rejected under 35 USC §112, first paragraph, for lack of written description. Claims 21, 25-31, 34, 37-44, 50-51, 54-60, 66, 72-73 and 76-82 were rejected under 35 U.S.C. § 103(a) as obvious over Degen in view of Chandler and Brown III. Claims 23-24, 35-36, 45-46 and 67-68 were rejected under 35 U.S. § 103(a) as obvious over Degen in view of Chandler and Brown III and further in view of Tonucci. The specific grounds for rejection set forth in the final rejection dated April 14, 2000, and applicants response thereto, are set out in detail below.

**Rejections under 35 USC §112, First Paragraph**

Claims 27-32, 35-37, and 40-82 are rejected under 35 USC § 112, first paragraph, for lack of written description. Specifically, the Examiner states that various terms recited in the claims are not supported in the specification of the application and the claims contain new matter. Additionally, the Examiner does not consider applicant's explanations of

support of specific numerical recitations to be convincing. Applicants respectfully traverse the rejection.

With respect to the recitation of the term "about," it is not clear to Applicant that the Examiner is rejecting the above recited claims for the recitation of "about." For example, claims 27 and 28 are not specifically noted by the Examiner as having alleged specific lack of support problems. The Examiner states that although "about" may be utilized in portions of the specification with particular dimensions, it does not support insertion of "about" with respect to all other dimensions. Applicant respectfully traverse the rejection based on this premise. The Examiner makes this rejection because he believes that the use of "about" in the claims represents new matter.

Applicant maintains that the specification provides ranges of diameters that the channels of the claimed device may be; for example, "0.1 - 10 micrometer diameter" (page 13, line 7); "as small as 33 nm or as large as several micrometers in diameter" (page 14, lines 10-11); "typically 450 nm" (page 15, lines 3); "300 nm" (page 15, line 9); "with pore diameters selected over the range from 2 nm to several micrometers" (page 18, lines 3-4); "approximately 2 nm to micrometer dimensions" (page 18, line 7); and "typically 0.2 μm" (page 19, lines 15-16). These ranges are from the lowest of approximately 2nm to about 2000μm, however, Applicant has chosen to claim a range of "about .033 micrometers to about 10 micrometers," as a preferred range within this broader range, and "about 0.45 micrometers to about 10 micrometers," as a more preferred narrower embodiment. Applicant maintains that the disclosure in the specification of these diameter ranges does "reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." The range conveys approximate numerical values within the range and the specific numbers that are claimed are specifically recited. The Examiner is also referred to the Preliminary Amendment filed on August 27, 1998, in which particular support for the amendments is provided on pages 9-12, providing additional support for the various dimensions of the substrate used in the claimed method. Further, the thickness of the substrate as being "between about 100 μm to about 1000 μm thick" is disclosed on page 8, line 15 for "about 100μm in thickness" and page 16, line 9 for "[o]btainable in thicknesses up to 1 mm." As noted in our response dated November 29, 1999, on pages 7 and 8, the channel cross sectional areas and channel inner surface areas recited in the claims are obtained by applying the formulae for the area

of a circle ($\pi r^2$) and for the inner surface area of a cylinder ($2\pi rl$), respectively. Because the values used to determine these areas are approximate; i.e., "about" or "approximately" or "up to" or "typically," these areas also are approximate.

Specifically in regard to claims 31, 51 and 73, the recited channel inner surface are obtained by applying the formula for the inner surface of a cylinder ($2\pi rl$) to channels having diameters 33 nm and 10μm and lengths (substrate thickness) of 100 μm and 1 mm. These dimensions are recited, for example as noted above, at page 13, line 7 (10 μm diameter), page 14, line 10 (33 nm diameter = .033 μm), page 14, lines 28-30 (100μm thick) and page 14, line 29 (1.0 mm thick = 1000 μm). Using the formula ($2\pi rl$), 2 x 3.14 x .033/2 μm (radius) x 100 μm = 10.362 $\mu m^2$ (about 10 $\mu m^2$) and 2 x 3.14 x 10/2 (radius) x 1000 = 31400 $\mu m^2$ (about 3 x $10^4$ $\mu m^2$), the specific range of the inner surface area of the channels is calculated. This calculation, using dimensions provided within the specification, supports the range of the inner surface area of the channels as recited in claims 31, 51 and 73. In view of these calculations that support previous and present arguments, it is maintained that claims 31, 51 and 73 are supported by the specification using recited dimensions and standard mathematical formula known to persons skilled in the art. Applicant also wishes to point out the allowed parent, U.S. 5,843,767, has claims that contain the same numerical language that is objected to by the Examiner.

Moreover, the skilled artisan readily would appreciate that the inventor had possession of the instantly claimed methods, which is the applicable standard for measuring compliance with the written description requirement of §112. Accordingly, the mere fact that the term "about" is not applied specifically to each and every one of the dimensions recited in the specification fails to support an assertion that the inventor did not have possession of the claimed methods that employ various compositions having "about" the recited dimensions. Accordingly, withdrawal of the rejection respectfully is requested.

For claims 37, 55, and 77, the Examiner asserts that the recitation of a "generic 'label' (claims 37, 55, 77) cannot be supported by recitation of certain species of a label." The Examiner notes that Applicant's reference to page 3, line 12, even if taken as supporting "label" generically, would at most support a labeling of DNA for hybridization reaction and not for labeling of other members, such as antibodies, or for the use of labeled DNA in other methods, such as sequencing. Applicant respectfully traverses because the specification specifically provides examples of radioisotope-, fluorescent-, and

chemiluminescent-labeled binding molecules and nowhere indicates that the claimed methods are limited to the use of such labels. Indeed, methods of labeling biological molecules are widely known in the art, and the skilled worker readily would appreciate that binding molecules to be used in the claimed methods can be labeled using any method known in the art. Moreover, the specification is replete with many examples of methods that use "labeled" biomolecules, in addition to the disclosure on page 3, line 12. For example, page 5, line 5 to page 6, line 2 discloses that "[o]rdinarily the microfabricated apparatus is used in conjunction with a known detection technology particularly adapted to discriminating between bounded regions in which binding has taken place and those in which no binding has occurred and for quantitating the relative extent of binding in different bounded regions." The disclosure discusses using the following: "[i]n DNA and RNA sequence detection, autoradiography and optical detection are advantageously used.....using $^{32}P$ or $^{34}S$ labelled samples." See page 5, line 8-10. The next paragraph discloses that in traditional sequencing fluorescent dye is covalently attached to DNA. Further page 9, lines 12-14, discloses various labels for polynucleic acids to detect hybridization. Thus, the specification provides a number of different types of labels and it is applicants position that this disclosure supports the term "label." In regard to labeling antibodies, Applicant believes that such labeling is well-known in the art, further demonstrating that one skilled in the art would recognize that the inventor possessed the claimed methods using "labeled" biomolecules. Applicant maintains that the specification and original claims 17-20 sufficiently supports and describes broadly, labels for polynucleic acids, as well as specific labels as in original claim 13, that support the generic term, "detectable label" used in claims 35, 55 and 77. For example, claim 17 provides that "...the detection of a binding reaction between said biomolecules in one or more of said regions and said test sample provides information capable of identifying the molecular species in the test sample;..." Skilled persons in the art would readily recognize that detection of the binding reaction would employ a label as a means of detection. A "patent need not disclose, and preferably omits, what is well known in the art." Hybritech v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed. Cir. 1986). Accordingly, withdrawal of the rejection respectfully is requested.

For claims 35, 47, and 67, the Examiner maintains that the terms "glass or silicon" remain unsupported and finds Applicant's reference to original claim 10 to be

unconvincing. Applicant respectfully disagrees with the Examiner because the specification contains numerous disclosures that the "substrate" or "novel flow-through genosensor" or "support wafers" are composed of "microchannel or nanochannel glass and porous silicon." See page 1, lines 18-22. Likewise, the description of Figures 1 and 3 on page 13, lines 6-10 and lines 16-17 disclose "glass" and "porous silicon," respectively. Example 1, beginning on page 14, line 6 discloses nanochannel glass wafers and Example 3, discloses porous silicon wafers (see page 17, line 14 to page 20, line 7). The Examiner comments that the claims recite channels without dimensions and that substrates with certain dimensions would not properly be considered porous. But it is noted that independent claim 21, for example, recites that the channels extend from the first major face to the second major face. Therefore, the channel provides a "pore" or opening from one side of the substrate to the other. Further, the detecting step requires that the sample binds with at least one binding reagent on the walls of at least one group of discrete channels in the substrate. For the method to function properly, the test sample must get into the channel, so therefore, the substrate must be porous. Further, page 8, lines 27-30, discloses that the substrate is used so that the test sample flows through the substrate. One of ordinary skill would know to exclude any possible materials which would render the claimed invention inoperative. See In re Geerdes, 180 USPQ 789 (CCPA 1974). Although an Examiner is permitted to read claim terminology broadly during prosecution, the Examiner may never read the claim language so broadly as to give a term an unreasonable meaning or a meaning inconsistent with the specification. In re Okuzawa, 190 USPQ 464, 466 (CCPA 1976). It is clear from the specification that only substrates in which the channels extend from first surface to the second surface. It is noted that the Advisory Action indicates that claims 21-26 and 32-34 are allowed. Claim 22 contains the terms "glass" or "silicon." In view of these arguments and numerous disclosures in the specification of the terms "glass" and "silicon" as useful materials for making the substrate, it is requested that the Examiner withdrawn this rejection.

The Examiner maintains the rejections to the format of claim 44, asserting that "[b]y not being limited to what the Examiner indicated claim 44 must be limited to, applicant has presented a claim which can encompass a new subgenus of assay methods not properly described in the original disclosure. Applicants respectfully traverse.

The Examiner's statements regarding lack of support for claim 44 are unfounded. The passage of U.S. 5,843,767 in column 8, line 59 is the same as the disclosures on page 4, line 25 to page 5, line 4 and page 12, line 25 to page 13, line 2 of the present specification. This passage describes that the substrates of the present invention are useful to perform a variety of tasks that include an analysis of patterns of gene expression by hybridization of cellular mRNA to an array of gene-specific probes, but also immunochemical analysis of protein mixtures, assay of receptor-ligand interactions and profiling of cellular populations involving binding of cell surface molecules to specific ligands or receptors immobilized within individual binding sites. Particularly, the specification recites that [a]lthough nucleic acid analysis is one principal use for such a microapparatus, it is advantageously applied to a broad range of molecular binding reactions involving small molecules, macromolecules, particles and cellular systems. Such molecules and particles may be the expression products of gene expression. Thus, the substrate of the present invention is envisioned to be utilized to measure molecules other than expression products that can be detected using gene-specific probes. In view of these arguments and the arguments made in the previous response that noted that the specification recites at page 9, lines 21-22 that "substantially homogeneous samples of a pre-determined set of biomolecules, each such sample being fixed in one or more of said regions" (emphasis added). Similarly, it also is clear that different regions may contain different binding reagents. See page 7, line 27 *et seq*. One skilled in the art would recognize that different binding reagents in different channels amount at least to first and second binding reagents. Accordingly, with respect to the rejection for lack of written description for first and second binding reagents, withdrawal of the rejection is respectfully requested.

With respect to claim 59, the Examiner asserts that Example 11 "disclosed only cDNA" and that therefore there "is no support" for the term "RNA." One skilled in the art is well aware that cDNA is the cognate DNA of an mRNA. Both the cDNA and the mRNA are capable of binding to a complementary nucleic acid strand in the fashion recited in claim 59. In any event, the specification at page 2, line 31, states that "...with samples containing an uncharacterized polynuclie acid, e.g., a cDNA, mRNA, recombinant DNA, polymerase chain reactions (PCR) fragments or the like..."; at page 4, line 27 and page 12, lines 26-27, states that "analysis of patterns of gene expression by hybridization of cellular mRNA."; at page 5, lines 8-9, states that "[I]n DNA and RNA sequence detection..." and

lines 22-23, states that "...when it is bound to duplexed DNA or RNA,..."; at page 11, lines 4-5, states that " if a sample of DNA or RNA is 'annealed' or 'hybridized' with a probe..."; and page 33, lines 5, states that "...[c]ytoplasmic RNA is extracted from cultured cells..." Applicant believes that he has provided sufficient support for the term "RNA" and it is maintained that claim 59 is literally supported in the specification and the rejection should be withdrawn.

The Examiner next maintains the rejection of claim 60 for the term "polynucleotides" somehow is "overbroad" which allegedly should be limited to cDNA which is the exemplified polynucleotide in Example 11. Applicant respectfully traverses this rejection. The specification makes it clear that in the preferred embodiment, the binding reagents that are immobilized on the walls of the channels in the substrate are nucleic acid sequences. For example, on page 24, line 20 to page 25, line 6, the disclosure shows that synthetic oligonucleotides or longer nucleic acid strands are attached to the glass surfaces. As shown in A Dictionary of Genetics, 5th Ed., pp 237 and 268, a oligonucleotide is a linear sequence of up to 20 nucleotides and a polynucleotide is a linear sequence of 20 or more nucleotides. It is believe that in view of the know definition of "polynucleotides" and the disclosure in the specification, the rejection should be withdrawn.

Next, the Examiner maintains that "there is no clear support for 'different conditions' in claim 63, since the specification allegedly recites only "different experimental conditions." Applicants have amended claim 63 to insert the term "experimental." Applicant does not agree that this amendment in any way further limits the claim but in an effort to address the Examiner's concerns, this amendment is made to utilize the exact language in the specification on page 13, line 29 that describes a depiction of the use of the claimed methods to "profile gene expression under different experimental conditions." Accordingly, the skilled worker readily would recognize that the applicant had possession of the invention recited claim 63 and the rejection should be withdrawn.

In regard to claim 64, Example 10 and Figure 5 disclose a mutation detection experiment, which particularly discloses the detection of mutations in the nucleotide sequence. The experiment on page 32, lines 1-6, shows that normal probes plus probes known to contain the mutations are included. It is believed that autoradiographs are compared to determine the mutations.

With respect to the rejection of claim 55, which the Examiner states should be claim 65, neither of these claims contain the language "first binding reagent" and "second binding reagent" for use in a method to detect "sequence variation." It is believed that the Examiner intended to reject claim 66 which does contain this language. Applicant believes that the specification on page 2, lines 12-26 discloses that the present invention allows the simultaneous conduct of a multiplicity of binding reactions on the substrate. The substrate contains "a set of discrete and isolated regions on the substrate, - such that each such discrete and isolated region corresponds to the location of one such binding reaction—in which each such discrete and isolated region contains an essentially homogenous sample of a biomolecule of discrete chemical structure fixed to such bounded region,--such that upon contact between the substrate and a sample...containing one or more molecular species capable of controllably binding with one or more of the pre-determined biomolecules,--the detection of the bounded regions in which such binding has taken place yields a pattern of binding capable of characterizing or otherwise identifying the molecular species in the test sample." Further, the specification on page 11, line 12 to page 12, line 24 disclose how one would use the substrate of the present invention for determining a sequence variation. The language of claim 66 requires that the method detects "a sequence variation in a least one gene." If the sequence variation is detected in two genes, then it is possible that the first and second binding reagent would be the same but two different test samples would be conducted on the substrate. Applicant believes that the claim is supported by the specification.

The Examiner further posits that "it is not clear where there is support for the method of claim 66 without the limitations of claim 70." This allegedly is so because Figure 5 and Example 10 show different binding reagents in different groups of channels. However, as noted above, it is clear from the specification that different groups of channels may contain the same binding reagent. See page 9, lines 21-22, stating that "substantially homogeneous samples of a pre-determined set of biomolecules, each such sample being fixed in one or more of said regions" (emphasis added). One skilled in the art would recognize that a mutation can be detected by applying different samples to two different groups of channels containing the same appropriate binding reagent. The presence of binding in one group of channels and of no binding in the other group is indicative of a

mutation. Accordingly, one skilled in the art would recognize that the applicant had possession of the claimed invention and the rejection should be withdrawn.

Finally, with respect to the rejections regarding the allegedly "unclear" derivation of certain claim terms, Applicant has already addressed each rejection to the claims containing the specific dimensions above and believes that each concern raised by the Examiner has been addressed.

**Rejections under 35 USC §103(a)**

Claims 21, 25-31, 34, 37-44, 50-51, 54-60, 66, 72-73 and 76-82 are rejected under 35 U.S.C. § 103(a) as obvious over Degen *et al.* ("Degen") in view of Chandler and Brown III. Claims 23-24, 35-36, 45-46 and 67-68 are rejected under 35 U.S. § 103(a) as obvious over Degen in view of Chandler and Brown III and further in view of Tonucci. Applicants respectfully traverse.

Degen in view of Chandler and Brown III

The Examiner maintains this rejection because the Examiner is not convinced that Degen is not applicable because no evidence or adequate explanations have been provided that Degen fails to disclose groups of channels. The Examiner maintains this rejection because he alleges that Degen is applicable as long as the present claims encompass an embodiment in which first and second binding agents are the same. The Examiner further alleges that there is nothing that distinguishes "a first group of channels" from "a second group of channels" and contends that the substrate of the present invention could be uniformly coated as in the disclosure of Degen. Applicant respectfully traverses this rejection.

Applicant's method utilizes a substrate that comprises (I) oppositely facing first and second major surfaces, (ii) a multiplicity of discrete channels extending through the substrate from the first major surface to the second major surface, (iii) at least a first binding reagent immobilized on the walls of at least a first group of channels, and (iv) at least a second binding reagent immobilized on the walls of at least a second group of channels. The important feature of the substrate used in the present method is the presence of "discrete channels" as illustrated in Fig. 1 of the present invention.

Degen describes a method for modifying membrane substrates for immobilizing "biologically active material." Degen's membrane is shown in Figs. 1 and 2 as element 10,

which as explained in column 15, lines 11- 34, is formed from a membrane material 12 which is preferably a supported membrane material, i.e., a membrane material in which a substrate is embedded. This membrane material is enclosed between coarser protective layers 14 and 16. The membrane element is arranged in the form of a pleated cylinder, having corrugations 18, surrounding a cylindrical or tubular perforated core 20. The membrane does not resemble Applicant's substrate. It appears that the analogous membrane is element 12 and in column 10, beginning on line 20, the biologically active membranes of Degen are described as formed by reacting the hydrophilic, microporous, skinless, activating agent-bound polyamide membrane, the chemically activated membrane with an acceptor molecule. In column 5, beginning at line 16, the membranes of Degen are more specifically described. In particular, lines 30-33, describe that a membrane that is particularly useful in the present invention is available from Pall Corporation under the trademark ULTIPOR N66. Applicant provides herewith a product sheet on syringe filters composed of the ULTIPOR® membrane as well as a comparison of NYLON 6 versus NYLON 6,6 from the Pall Corporation website (assignee of Degen). This latter product sheet describes the NYLON 6,6 filter as a PVDF filter.

Applicant also provides an article from *The Scientist* 12(19):18, Sep. 28, 1998 that shows a PVDF membrane and discusses it on page 2 in the marked paragraph. The electron micrograph, as well as the disclosure, shows that the process for preparing these membranes results in "channels and cavities form in the material, surrounded by blobs, fibers, and microscopic sheets of polymer." Thus, it is Applicant's contention that the Degen filter and the substrate in the claimed method are not the same, and Degen's polyamide membrane does not contain discrete channels.

Applicant also refers to the arguments that he made in his previous response regarding Degen's description of a membrane that is uniformly coated with the "biologically active material" and conspicuously fails to suggest depositing biologically active material in groups of channels in the membrane. Indeed, the membrane design described in Degen would make this task essentially impossible (see Figure 1),and therefore Degen teaches *away* from Applicant's claimed invention. For the reasons set forth above, Degen neither teaches nor suggests the instantly claimed methods, which use a substrate where the binding reagents are deposited in distinct groups of discrete channels.

This deficiency is not cured by Chandler, which describes methods of carrying out multiple assays on separate filters, *i.e.* individual assays each are carried out on a separate filter. The membrane-bound assays described by Chandler are conventional. See column 2, lines 65-67. Nowhere does Chandler teach or suggest methods of carrying out binding assays in channels or groups of channels on the same substrate, nor does Chandler suggest immobilization of binding reagents on the walls of channels in the substrate. Moreover, Chandler fails to teach or suggest methods using two or more different reagents in two or more groups of channels. Brown also cannot cure the deficiencies of Chandler and Degen, merely stating that various types of ligands and receptors can participate in binding reactions "like those involved in immunoassays."

In sum, for the reasons set forth above, Degen's membrane is different from the substrate of the present method and the cited references may not properly be combined. Moreover, even if combined, the references fail to teach or suggest the instantly claimed invention. Accordingly, the rejection is improper and should be withdrawn.

Degen in view of Chandler and Brown III further in view of Tonucci

The Examiner states that Tonucci teaches use of nanochannel glass filters, that the membranes of Degen are "functional" equivalents of Tonucci's filters, and that it would have been obvious to use the Tonucci filters in the assays taught be Degen. Applicants respectfully traverse.

The deficiencies of Degen, Chandler, and Brown III are described in detail *supra*. Tonucci, which merely describes nanochannel glass and its use as a filter cannot cure these deficiencies. In filtration methods, the material to be filtered is applied uniformly to the filter to achieve optimal filtration. Thus, by describing use of nanochannel glass as a filter material for separations and thereby suggesting the uniform application of a material to the filter Tonucci, like Degen, teaches away from the claimed invention, where binding reagents are deposited in distinct groups of channels on the substrate. Accordingly, the cited references fail to teach or suggest the instantly claimed invention, and the rejection is improper and should be withdrawn.

## CONCLUSION

In view of the above remarks and amendments, it is respectfully requested that this amendment after final be entered. Applicant believes that the application is in condition for allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to telephone the undersigned at the number listed below if the Examiner believes such would be helpful in advancing the application to issue.

Respectfully submitted,

February 16, 2001
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